CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

TUBERCULOSIS INFORMATION

- Treatment of Tuberculosis Disease in Non–HIV-Infected Persons

The initial phase of treatment for tuberculosis is crucial for preventing the emergence of drug resistance and determining the ultimate outcome of the regimen. Four drugs — isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin — should be included in the initial treatment regimen until the results of drug susceptibility tests are available. If there is little possibility of drug resistance (i.e., less than 4% primary resistance to isoniazid in the community and the patient has had no previous treatment with TB drugs, is not from a country with a high prevalence of drug resistance, and has no known exposure to a patient with drug-resistant disease), three drugs (isoniazid, rifampin, and pyrazinamide) may be adequate for the initial regimen.

There are several options for daily and intermittent therapy, but the aim of treatment should be to provide the safest and most effective therapy in the shortest period of time. Given adequate treatment, almost all patients will become bacteriologically negative, recover, and remain well.

For each patient with newly diagnosed TB, a specific treatment and monitoring plan should be developed in collaboration with the local health department within 1 week of the presumptive diagnosis. This plan should include a description of the treatment regimen, the methods of assessing and ensuring adherence to the anti-TB regimen, and the methods of monitoring for adverse reactions.

There are several regimen options for non–HIV-infected persons (Table 1). Dosage recommendations are listed in Table 2.

Table 1
Regimen Options for the Treatment of TB in Non–HIV-Infected Children and Adults

Option 1	Option 2	Option 3
Initial Phase Daily isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin for 8 weeks. Ethambutol or streptomycin may be discontinued if TB is susceptible to isoniazid and rifampin. Ethambutol or streptomycin may not be necessary for patients in areas where isoniazid resistance is very low (<4%). Continuation Phase If TB is susceptible to isoniazid and rifampin, give isoniazid and rifampin for 16 weeks, either daily, two times weekly, or three times weekly.*	Initial Phase Isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin daily for 2 weeks, then two times weekly* for 6 weeks. Continuation Phase If TB is susceptible to isoniazid and rifampin, give isoniazid and rifampin two times weekly* for 16 weeks.	Isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin three times weekly* for 6 months.
For all patients, consult a TB medical expert if drug susceptibility results show resistance to any of the first-line drugs or if the patient remains symptomatic or smear or culture positive after 3 months.		

*Directly observed therapy must be used with all regimens administered two or three times weekly.

Table 2

Dosage Recommendations for the Treatment of TB in Non-HIV-Infected Children* and Adults

Drugs	Dose in mg/kg [Maximum Dose]					
	Daily		Twice-Weekly		Thrice-Weekly	
	Children	Adults	Children	Adults	Children	Adults
Isoniazid	10-20 [300 mg]	5 [300 mg]	20-40 [900 mg]	15 [900 mg]	20-40 [900 mg]	15 [900 mg]
Rifampin	10-20 [600 mg]	10mg/kg [600 mg]	10-20 [600 mg]	10 [600 mg]	10-20 [600 mg]	10 [600 mg]
Pyrazinamide**	15-30 [2 gm]	15-30 [2 gm]	50-70 [4 gm]	50-70 [4 gm]	50-70 [3 gm]	50-70 [3 gm]
Ethambutol***	15-25	15-25	50	50	25-30	25-30
Streptomycin**	20-40 [1 gm]	15 [1 gm]	25-30 [1.5 gm]	25-30 [1.5 gm]	25-30 [1.5 gm]	25-30 [1.5 gm]

* Children 12 years of age or younger

** Should not be used in pregnant women.

*** Ethambutol is not recommended for children who are too young to be monitored for changes in their vision. However, ethambutol should be considered for all children who have TB that is resistant to other drugs but susceptible to ethambutol. No maximum dosages for EMB but in obese patients dosage should be calculated on lean body weight.

Special Situations

Extrapulmonary TB. As a general rule, regimens that are adequate for treating pulmonary TB in adults and children are also effective for treating extrapulmonary disease. However, infants and children who have miliary TB, bone and joint TB, or TB meningitis should receive a minimum of 12 months of therapy.

In patients with extrapulmonary TB, the type of follow-up examinations should be determined by the site of the disease. Bacteriologic evaluation may be limited by the relative inaccessibility of the site. Thus, the response to treatment must often be judged on the basis of clinical and radiologic findings.

Pregnant or Lactating Women. Pregnant women with TB must be given adequate therapy as soon as TB is suspected. The preferred initial treatment regimen is isoniazid, rifampin, and ethambutol (ethambutol may be excluded if primary isoniazid resistance is unlikely). **Streptomycin should not be used because it has been shown to have harmful effects on the fetus**. In addition, pyrazinamide should not be used routinely because its effect on the fetus is unknown. Because the 6-month treatment regimen cannot be used, a minimum of 9 months of therapy should be given. To prevent peripheral neuropathy, it is advisable to give pyridoxine (vitamin B_6) to pregnant women who are taking isoniazid.

The small concentrations of TB drugs in breast milk do not have a toxic effect on nursing newborns, and breastfeeding should not be discouraged for women undergoing anti-TB therapy. Similarly, drugs in breast milk should not be considered effective treatment for disease or infection in a nursing infant.

Children. The treatment of TB is essentially the same for children and adults. In infants, TB is much more likely

to disseminate; therefore, prompt and vigorous treatment should be started as soon as the diagnosis is suspected. Ethambutol is not recommended for children who are too young to be monitored for ocular toxicity (children younger than 8 years). Twelve months of therapy is recommended for children with miliary disease, bone and joint disease, or meningitis. Children who have tuberculous meningitis should be treated with 2 months of daily isoniazid, rifampin, pyrazinamide, and streptomycin, followed by 10 months of daily or twice-weekly isoniazid and rifampin.

Isoniazid-Resistant TB. A 6-month regimen of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin is effective for the treatment of TB resistant only to isoniazid. When isoniazid resistance is documented during the recommended initial four-drug therapy, isoniazid should be discontinued and the other three drugs should be continued for the entire 6 months of therapy. TB resistant only to isoniazid may also be treated with rifampin and ethambutol for 12 months.

Multidrug-Resistant TB. It is more difficult to treat TB that is resistant to isoniazid and rifampin than it is to treat drug-susceptible TB. Therapy for TB resistant to isoniazid and rifampin must continue for 18 to 24 months after the culture becomes negative for *Mycobacterium tuberculosis*. Also, the drugs used to treat drug-resistant TB are less effective and more likely to cause adverse reactions. Clinicians who are not experienced in treating drug-resistant TB should seek expert consultation from the state or local health department.

Adverse Reactions

Adverse reactions to TB drugs are relatively rare, but in some patients they may be severe. Clinicians who treat TB should be familiar with the methods of monitoring for adverse reactions and response to treatment. In some situations (e.g., drug-resistant TB, pregnant patients, HIV-infected patients), expert consultation may be required. Before starting therapy, adults should have baseline laboratory tests, and adults and children who are taking ethambutol should have a baseline examination of their visual acuity.

During therapy, clinicians should monitor patients for side effects. They should instruct patients to look for the side effects commonly associated with the drugs they are taking. Also, clinicians should see patients at least once a month to assess whether they are having side effects.

Patients who remain symptomatic or smear or culture positive after 2 months should be carefully reevaluated, and drug susceptibility tests for these patients should be repeated. Clinicians should consult a TB medical expert if the drug susceptibility results show resistance to any of the first-line drugs.

Case Management

One strategy that may be used to ensure that patients complete TB treatment is case management. There are three elements of case management: assignment of responsibility, systematic regular review, and plans to address barriers to adherence. In case management, a health department employee (case manager) is assigned primary responsibility and is held accountable for ensuring that each patient is educated about TB and its treatment, that therapy is continuous, and that contacts are examined. Some specific responsibilities may be assigned to other persons (e.g., clinic supervisors, outreach workers, health educators, and social workers).

A component of case management that helps to ensure that patients adhere to therapy is directly observed therapy (DOT). DOT means that a health care worker or another designated person watches the patient swallow each dose of TB medication. DOT ensures an accurate account of how much medication the patient really took. DOT should be considered for all patients because clinicians are often inaccurate in predicting which patients will adhere to medication on their own. However, it takes good case management in concert with DOT to really make DOT programs effective.

It is important that DOT be carried out at times and in locations that are as convenient as possible for the individual patient. Therapy may be directly observed in a medical office or clinic setting but can also be observed by an outreach worker in the field (i.e., the patient's home, place of employment, school, or other mutually agreed-upon place). In some situations, staff of correctional facilities or of drug treatment programs,

home health care workers, maternal and child health staff, or designated community members may provide DOT.

Monitoring Adherence

Pill counting and urine tests have been used to assess whether patients are adhering to therapy for TB. However, the only way to ensure that patients take every dose is to use directly observed therapy.

For More Information

For more information about implementing CDC guidelines, call your state health department.

To order the following publications, call the CDC's Voice and Fax Information System (recording) toll free at (888) 232-3228, then press options 2, 5, 1, 2, 2 (Note: You may select these options at any time without listening to the complete message). Request the publication number of the document you would like to order. You may also visit the Division of TB Elimination's Web site at www.cdc.gov/nchstp/tb.

Publication # 00-6453. American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994;149:1359-1374.

Publication # 99-5879. CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *MMWR* 1998;47(No. RR- 20).